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(54) Pharmaceutical uses of ondansetron

(57) Pharmaceutical compositions of the 5HT antagonist ondansetron for use by civilians or the military in warfare or emergency situations e.g. in the prevention or treatment of seasickness, airsickness, space sickness, dehydration, battle fatigue, combat stress reaction, for protection against chemical warfare agents such as nerve gas, nausea and post-traumatic stress disorder. The active agent is preferably in the form of a chewing gum.

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Title: Safety enhancing pharmaceutical compositions

The present disclosure relates to pharmaceutical compositions of ondansetron and articles of manufacture containing them whose purpose is to reduce the risk to and increase the safety of persons during times of exposure to extreme physical danger, or increase the safety of persons likely to be exposed to danger.

More particularly the disclosure provides methods of using, delivering and storing pharmaceutical compositions of the agent ondansetron intended for use by otherwise fit and healthy persons in circumstances of grave danger or in circumstances where danger might be or is liable to occur.

The invention is further extended to find a use in the prevention or treatment of the effects of SOMAN or other toxic nerve gas or chemical agent, and to other uses in a theatre of war.

Theoretical Background

The substance 'ondansetron' was first described as a racemic mixture of 1:1 of R(+) and S(-) isomers of 1,2,3,9,-tetrahydro-9-methyl-3-[2-methyl-IH-imidazol-1-yl)methyl].4H-carbazol-4-one, disclosed in US 4,695,789; and GB 2 153 821 A; and EP 0 226 266 A2; disclosed and incorporated fully herein by reference, and hereafter referred to as simply ondansetron.

Ondansetron is widely accepted to be a potent 5HT, serotonin, inhibitor. Having a dual site of action in the ilium and more centrally in the area postrema. Ondansetron is an agent used to treat the nausea associated with chemotherapy and radiotherapy - the treatment of cancer. It is believed that radiotherapy and chemotherapy cause the release of 5HT by the enterochronaffin cells in the gut, thus producing intense nausea.

The use of ondansetron in the treatment of cancer associated nausea was disclosed in US pat. nos 4,753,789 and U.S. pat. 4,929,632 and elsewhere in the literature see especially Cunningham D et al, Lancet 1987; 1;1461-3 and De Haan L D et al, Eu. J. of Cancer and Clin. Oncol; 1988; 24: 1383-4 and also Priestman T.J. Eu. J. Cancer and Clin. Oncol. 1989; 25; (Suppl 1): 529-533 disclosed and incorporated herein by reference.

All previous disclosures and publications relating to ondansetron are exclusively concerned with the use of ondansetron in a hospital or clinical context, the treatment of those persons suffering from an illness especially cancer. Previous disclosures also propose ondansetron as an agent useful to treat mental illness especially schizophrenia.

The present application differs in that the disclosed use of ondansetron will be by persons in robust health, at the peak of physical fitness and mental fitness, and by persons generally.

The application further discloses that ondansetron will be the form of compositions suitable for use during times of extreme physical danger. The application still further discloses that the compositions containing ondansetron will be packaged as articles of manufacture suitable for rough handling during storage or transport as would be expected in combat or times of emergency.

Within the armed forces it is widely known that pilots have a distinct personality profile.

Retzlaff and Gibertini first described the pilot personality of military aviators as being the "right stuff" for the Airforce. This personality subtype has been the subject of intense research and one is directed to Picano J et al, Aviation Space and Environ. Med June 1991; 62:517-520 for a recent review. Briefly airforce pilots are described as outgoing, competitive, less introspective, less sensitive, and less self effacing than non-flyers. Airforce pilots are at the extreme end of mental and physical fitness.

The present disclosure differs from previous disclosures in that it teaches the use of compositions of ondansetron and materials of manufacture for delivery of said compositions to airforce pilots and other persons of robust physical and mental health.

The prior art WO93/00074 and WO93/00075 Sepracor Inc.; together with U.S. Pat. No. 4,695,578 and US Patent No. 4,847,281 disclosed and incorporated fully herein by reference, describe and teach the use of ondansetron to treat the sick, in schizophrenia, in depression, psychosis, cancer, chronic anxiety disorders, depression, migraine, substance abuse.

It should be noted that none of the above mentioned sickness particularly schizophrenia or substance abuse would be compatible with a military career or as a pilot in the Airforce.

Accordingly it is stressed that the present disclosure teaches the beneficial use of ondansetron compositions to assist physically fit persons in special circumstances provoked by occasions of exceptional demands.

Space flight both in space and in training aircraft such as NASA KC-135 expose pilots to fluctuating G forces over a large range. In shuttle missions space motion sickness was recorded as incapacitating 71% of astronauts, Jennings R T et al. Aviat. and Space Environ. Med. 1988; 1988, 59; 448-510.

Space motion sickness has so far defied adequate explanation but represents a major hazard for astronauts. It has been suggested by P. DiZido et al. Aviat. and Space and Env. Medicine 1991; April; 300-7; that the mechanism may be velocity storage and dumping by the saccus and uticide, caused by unnatural combinations of G forces such as those which can only be produced by a vehicle.

Airsickness is a major financial drain for the Airforce. The incidence of airsickness ranges from 14.6% of student pilots showing severe airsickness, see Dobie T G AGARD/NATO

1974; AGARD-AG-177 to 24% of students during early jet training, Hartzell WG. CSURG: AIR-COM Winipeg 1979.

60% of airsick trainees would be expected to drop out at a cost to the Airforce of between $15,000 to $500,000 per pilot trainee depending on the stage of dropping out; Jones D R et al Aviat. Space Environ. Med. 1985; 56:1152-7. So great are the costs especially when airsickness strikes a trained pilot that the Airforces of NATO have a number of remedial programmes as described by Banks R D, Aviat. Space and Environ. Med, Dec 1992; 63:1098-1101. These remedial programmes are not always successful and are themselves extremely expensive. Indeed sickness can also occur in a simulator termed "simulation sickness" in as many as 60% of subjects.

Simulator time is expensive. Moreover simulator sickness is difficult to predict. Persons with no previous experience of motion sickness may fall victim to simulator sickness. Newer specialized questionnaires are helpful, see Kennedy R S, Aviat. and Space Environ. Med, 1992; 63:588-93 nevertheless valuable simulator hours are often lost due to this problem.

In fighter jets airsickness may be dangerous. Spacial disorientation may occur suddenly, be quite incapacitating and accounts for up to 20% of air accidents.

The loss of natural visual sensory signals especially when a pilot must fly by instrument can lead to rapid unpredictable incapacity compromising safety. The testing of this condition and the implications for air safety are discussed by Clarke J B et al, Aviat. Space and Environ. Medicine, Oct. 1992; 63:914-8.

Of course nausea is not a problem confined to military aviators but occurs also in the civil aircraft. Studies carried out by IATA International Air Transport Association and by IFALPA International Federation of Airline Pilots Association report nausea to occur in 14.0% of incapacitating incidents. Green J et al, Aviat. Space Environ. Med. 1991, 62:1068-72.

Of major concern to military aviators is the problem of toxic nerve gas or other chemical or biological weapons. A major class of neurotoxins are "chlorinergic neurotoxins" and in particular SOMAN® a nerve gas and a potent neurotoxin acting as a cholinesterase inhibitor. Inhalation of even small quantities of SOMAN leads to convulsions and death. However, Olney J W discloses in US Patent 4,988,710 and also in U.S. Patent no. 5,001,583 the use of agents scopolamine, benaclyzine benztropine, procyclidine and similar compounds to obtain agents capable of reducing or ameliorating the dangers of nerve gas.

Currently Pyridostigmine Bromide is used as a pre-treatment where nerve gas exposure is a possible hazard. However, a major side effect of Pyridostigmine Bromide (PB) is gastrointestinal upset. As previously mentioned gastrointestinal upset may be lethal for pilots. Pyridostigmine Bromide (PB) has many side effects.

The studies on PB use in US Airforce pilots and air crew may be found in, Wiley R W et al, Aviat. and Space and Environ. Med. 1992; 63: 1054-9.

The use of Pydridostigmine Bromide is not confined to the Airforce but also finds a place in land based troops. A further side effect of PB is it's disruption of thermoregulation. Greater levels of exertion are required of infantrymen who may quickly become dehydrated. Vomiting as a side effect of PB will be worsened by dehydration which will in turn worsen the dehydration: See Wegner B C et al Aviat. Space Env. Med., 1992:63:37-45. These problems will be further worsened by biological and chemical protective clothing. Vomiting whilst wearing protective clothing into the clothing will lead to it becoming extremely uncomfortable, unwearable or even be removed to vomit thus leading to exposure to nerve gas. Accordingly it will be appreciated that troops exposed to nerve gas or in a chemical warfare theatre must not vomit at all costs.

The present disclosure teaches the use of ondansetron either on it's own or in conjunction with Pyridostigmine Bromide or another carbamate as a pre-treatment for nerve gas

intoxication in warfare or for military use, both by airforce personnel, ground base troops and the navy.

The problem of combat stress is yet another problem confronting airmen but in a particular way.

Combat stress is now accepted to affect not only the 'flyers' but all other air base personnel. A reason for this broadening of exposure to combat stress is targeting of air bases by enemy fire by missiles and by CBW agents chemical and biological warfare agents.

Airmen are unique in being required to be sitting targets both in the air and on the ground. Moreover the family members of air crew live on base and are exposed to the same stressors further compounding the problem. A further factor is "body handling". Airmen are exposed to other forces casualties and mortalities in large numbers. It is the air crew who must transport casualties and fatalities in bodybags to home base.

The stresses of these situations may lead to bad performance, grounding, or permanent psychological dysfunction, see Rundell J et al. Military - Medicine Vol 155, Nov. 1990; 11, 515. The present disclosure teaches the use of ondansetron in these situations and more generally as a prophylaxis against combat stress in the airforce.

Among ground troops it is widely accepted that combat stress reaction, CSR, accounts for 30% to 40% of all casualties needing evacuation. For instance during the 1973 Yom Kippur War, 900 of the first 1500 casualties in the border site were CSR victims. Mareth T R et al, Milit. Med. 150: 186-90, 1985.

It is known that "gas hysteria" or the threat of chemical attack can greatly aggravate the problem. Kentsmith D K Milit. Med, 151:89-96, 1986. CSR can occur quickly and requires prompt assessment and management, to prevent the individual being a danger to himself and others, Schaub M R, Capt. Milit. Med. 155; 11; 539; 1990.

Observations by Capt. B. McCaughey of the Allied Forces on the effects of "battle fatigue", another term for combat stress reaction are most pertinent. McCaughey points out that operation desert storm - the Persian Gulf war may have been won in part by the lower incidence of battle fatigue among US and UK troops. He observes that the Iraqi forces were plagued by combat stress reaction by it's associated dehydration, apathy and inability to fight. Thanks to careful preparations the US forces were well prepared for combat stress.

McCaughey further observes that future conflicts may be "come as you are" events allowing no time for psychological preparation. McCaughey further emphasises the need for continued study of all measures that may be useful in combating battle fatigue, McCaughey, Brian Capt. Milit. Med., Vol 156; 1991, 694-695. McCaughey warns military planners that for future wars other measures, (such as drugs), in place of lengthy psychological preparation, will be needed.

Accordingly the present disclosure provides ondansetron and compositions thereof as useful agents in the prevention of battle fatigue, CSR. The safety enhancing compositions of the present disclosure are therefore all the more useful because of the low side effect profile of ondansetron which will not reduce a soldiers ability to fight.

Not infrequently troops are transported by sea to the active theatre. Gastro intestinal symptoms may render troops unfit and more liable to CSR on disembarkation. This is a special problem for marines.

The present compositions will improve troop readiness in such situations.

The agents of the present disclosure are not intended exclusively for the military but also for civilians.

In the case of maritime disasters, 75% of TEMPSC occupants (totally enclosed motor propelled survival craft) experience nausea, worsening their dehydration and endangering

safety, J.P. Landolt et al, Aviat. Space Environ. Med., 1992; 63: 219-25. TEMPSC are the life boats of choice on all modern ships.

There is a very real danger of dehydration if seasickness in TEMPSC vessel remains uncontrolled. Rescue from a TEMPSC vessel may be delayed for days. Effecting a rescue in bad weather takes far longer than most people anticipate. Dehydration is a killer in these circumstances.

Similar dangers occur on small yachts. Owners may put to sea with a small crew of one or two persons or even no crew. An unexpected change in weather produces a seasickness of two distinct varieties;

Variety (1) The victim may vomit but is thereafter relieved.

Variety (2) The victim goes through a prolonged period of nausea accompanied by apathy.

In the second variety or syndrome of seasickness it is the apathy which proves lethal.

So great is the apathy that the yachtsman loses the motivation to navigate properly.

Very quickly the yachtsman will have lost his position which in addition to the apathy a loss of motivation to sail properly can prove fatal.

Further it will be appreciated that flying on long haul civil aircraft leads to dehydration; and that in the event of an aircraft ditching over sea, surviving passengers would have their survival chances further reduced by vomiting. The use of the articles of manufacture of the present disclosure may be extended from military use to civilian use in search and rescue, for carriage by all TEMPSC vessels, by all airlines and their safety craft, in all airlines with life vests; in all small boats and yachts, and in emergency kits.

BRIEF SUMMARY

The present disclosure provides pharmaceutical compositions of ondansetron as articles of manufacture. The substance ondansetron is a potent 5HT antagonist.

The compositions of ondansetron as articles of manufacture provided by the present disclosure are for intended use by healthy rather than by the infirm.

More particularly the compositions of ondansetron, the said articles of manufacture, will be useful to the armed forces, to reduce space sickness, airsickness in fighter pilots, combat stress reaction or battle fatigue. The compositions may also be used a prophylaxis or pretreatment against CBW agents (chemical and biological warfare) agents and in this circumstance may be used alone or in conjunction with carbamates especially PB pyridostigmine bromide.

The disclosure extends to civilian use especially in connection with disasters.

The articles of manufacture, pharmaceutical compositions, may be included as an integral part of life rafts; airline life vests; small boat and yacht emergency kits, or as part of life boats or any other rescue vessel.

It will be appreciated that the intended use of the said pharmacological compositions will occur in circumstances of extreme physical danger or when danger may occur and their use will be by otherwise healthy fit persons such as military personnel.

It will also be appreciated that the articles of manufacture comprise pharmaceutical compositions of matter of ondansetron packaged in containers suitable for rough handling and suitable for use in a theatre of war or during an emergency. The packaging component of the said article of manufacture may look different from that normally found in clinic or in hospital or that normally associated with the care of the infirm.

DETAILED DISCLOSURE:

The present invention discloses articles of manufacture comprising pharmaceutical compositions of ondansetron and their packaging intended for special purposes and whose use will not be in a clinic or hospital to treat or by the sick but whose use will be by physically fit military personnel or sportsmen and special employees in circumstances of physical danger or where danger is anticipated, or possible, or persons generally who might be in danger. The use of the articles of manufacture herein disclosed will enable those at risk to cope with physical danger more efficiently. The articles of manufacture are further likely to enhance safety by preventing the occurrence of inefficiency or poor performance provoked by combat stress reaction, battle fatigue, space sickness, simulator sickness, airsickness in civil aircraft or in military jets during training or on missions, seasickness in transport vessels, seasickness in yachts, seasickness in survival craft, past traumatic stress disorder.

The term "combat stress reaction" otherwise known as "battle fatigue" be taken herein to mean that loss of soldiers efficiency, often temporary, accompanied by lack of motivation to soldier, gastrointestinal disturbances, lethargy, disorganisation and sometimes a sense of hopelessness. This often short lived and easily treated constellation of psychological symptoms may often be successfully treated with counselling and rest, however, their appearance in a combat situation may represent a hazard to both the victim and other troops who depend on him. The articles of manufacture of present disclosure make combat stress reaction a less likely occasion. Therefore it is envisaged that the present agents will be used by troops both before any danger exists or before any manifestation of combat stress reaction appears, as well as during a dangerous situation in combat or afterward as a treatment of combat stress reaction, to mitigate it's effects or reduce it's duration, or to prevent its occurrence.

The term "space sickness" be taken to mean that variety of space motion sickness associated with loss of efficiency and sometimes but not always, nausea and vomiting

which may develop in space craft or space training craft or other vehicles where trajectory of motion may be 360°.

The term "airsickness" be taken to mean that constellation of psychological symptoms with or without nausea and vomiting which may take place in military jets during fluctuating G force manoeuvres or during fly by instrument missions or dog fights. When the symptoms arise during simulator training the condition will be known as "simulator sickness". The articles of manufacture may be used also to treat the fear of flying in civilian aircraft. They may also be used to treat claustrophobia in aircraft. The articles of manufacture are also intended for administration to nervous passengers during turbulent flights or emergencies. The articles of manufacture may also be used to treat or prevent toxic nerve gas poisoning either used on their own or in combination with other agents particularly carbonates and more particularly (PB) Pyridostigmine Bromide.

The term "seasickness" as used herein is often but not always, accompanied by nausea or vomiting. In many instances a sailor or yachtsman experiences fatigue, lethargy, apathy, intense tiredness, and a feeling of being "washed out" with no nausea or vomiting. The articles of manufacture as disclosed herein are not solely directed to prevent or treat the nausea and vomiting which may sometimes be a feature of seasickness but are directed against those other symptoms lethargy and reduced efficiency which are more dangerous and may be lethal in totally enclosed motor propelled survival craft TEMPSC or where small yachts are crewed alone or by only one or two people.

The articles of manufacture for the intended disclosed uses will encompass pharmaceutical compositions of the racemic mixture of 1:1 R(+) and S(-)ondansetron whose manufacture was disclosed in US Patent No. 4,695,578 and incorporated fully herein by reference.

Whilst the present disclosure envisages special preferred embodiments, the existing preparations of ondansetron may be used as the said articles of manufacture with certain desirable modifications.

Where ondansetron is in tablet form it is preferable that the composition be ondansetron 8mg, range 1-20mg compressed with 492mg filler such as milk powder or starch range 480-499mg to produce tablets of 500mg dry weight. This composition is heavier than that in current clinical use. It should be flavoured with peppermint. However, for use at sea rather than in hospital, the composition should be individually wrapped in foil and plastic wrapping. Moreover, it should be chewed not swallowed for two effects; to allow faster buccal absorbtion; and to prevent accidental inhalation. Inhalation of tablets is a serious risk at sea in a moving vessel and could cause death by choking. In the case of military aviators or combat troops where ondansetron is intended for use in the prevention of nerve gas poisoning, the tablet should be chewed half an hour before the preventive effect is desired.

Preparation of ondansetron formulated as suppositories may also be used however, they suffer from the drawbacks of difficult access in shellsuits and problems with hygiene and acceptability in emergency situations. They may be used in spacecraft. However, their use in maritime or combat settings is less than ideal.

Preparations of ondansetron formulated as aerosols are undesirable in aircraft, spacecraft and emergency vessels. Moreover, the duration of action is too short.

The disclosure will now be illustrated by reference to the following preferred exemplary embodiments which are intended to be non-limiting and variations of which embodiments being obvious to the skilled artisan being considered to fall within the scope and spirit of the disclosure.

Example 1

The greatest problem to overcome in pharmacology is compliance, being defined as a person's willingness to consume an agent. There is little point in offering an agent for consumption to a consumer who perceives the agent or article of manufacture to be at odds with his personality or psychological state.

The dominant psychological state of combat troops, military aviators or astronauts or yachtsmen, and the like, is that of the "macho" personality.

The physically fit "macho" combat troops will find, tablets, suppositories, injections, inhalers and other clinical preparations of ondansetron as unacceptable or undesirable. Troops may consider it "sissy" to take tablets before combat. Tablets may even damage morale.

However, chewing gum is strongly associated with the tough "macho man" image. Moreover, chewing gum is less likely to be inhaled at sea or in the air. Further, chewing gum permits a slow release of agent, useful during intermittent vomiting. Still further, chewing gum permits a greater degree buccal absorbtion of active agent. Still further, chewing gum carries the additional benefit of equilibration of middle ear air pressure. Still further, chewing gum carries psychological benefits in the mechanical act of chewing.

A further particular advantage of chewing gum is it's action as a sialagogue, salivary flow stimulant. This feature is important for applications during times of dehydration or unavailability of water.

Swallowing a tablet dry whilst in a survival craft without water to flush the tablet down will lead to an unpleasant sensation of choking and food sticking in the oesophagus.

For these reasons, chewing gum is preferred.

Preferred formulations of chewing gum for the delivery of ondansetron, but by no means the only formulations, will employ the agent polydextrose. Polydextrose is a polyol, a polymer of dextrase whose method of preparation is disclosed in US Patent No. 3,766,165 Pfizer Inc. Polydextrose is a bulky agent of low calorific value which improves texture of foodstuffs. Polydextrose is non-cariogenic, an important consideration in circumstances of vomiting where acid has already stripped enamel.

The use of polydextrose in chewing gum is disclosed in EPO Patent No. 0,252,974, US Patent No. 4,765,991 and EPO No. 0,398,465 and US Patent No. 5,066,511 and JP No. 86,173,748 and US Patent No. 4,382,963 incorporated fully herein by reference. One is especially directed to WO 92/08370 Wrigley Inc. for a disclosure of the use of polydextrose as a bulk sweetener.

Polydextrose is marketed in two forms, Polydextrose A, a form containing citric acid and exhibiting a pH of 2 - 3.5 in aqueous solution.

Polydextrose A is especially useful for the delivery of ondansetron hydrochloride. The acidic ondansetron becomes more lipophilic when used with polydextrose A the ondansetron should be placed in the surface coating of the chewing gum to avoid excessive partitioning of ondansetron into the fat and resin texturing components of the chewing gum bulk.

Polydextrose A may be melted at 130° C with sorbitol or xylitol dried and crushed to a fine powder. Ondansetron power is then mixed with this powder in a mixer.

The resultant mix may be used to coat a chewing gum or as a dusting powder, providing an immediate availability of ondansetron.

The second form of polydextrose "Littesse" trade name has the citric acid content much reduced. In this form it may be added to chewing gum as a bulking agent either as a solid or syrup. Ondansetron mixed with "Littesse" in this form is designed for slower release during the process of chewing the gum. It must be remembered that ondansetron will tend to partition into the terpene resins, or other fats in the chewing gum. Therefore, terpene resins, beeswax, and lipids must be kept to a minimum in the gum formulation or substituted for by polyisobutylene, isobutylene-isoprene copolymer or styrene butadine rubber or chicle or the like. It will be appreciated that ondansetron may be administered by a chewing gum formulation as part of the centre fill liquid, wherein 1% to 20% of gum

weight is central fill liquid, or administered as part of the rolling compound 1 - 3% gum weight is rolling compound.

Polydextrose bulk sweetener and ondansetron may be encapsulated agglomerated or absorbed, in accordance with the known art of chewing gum manufacture, and thereafter the combined polydextrase and ondansetron will be treated as bulk sweetener.

Example Preparations:

Example 1

Chewing gum weight percentage of ingredients

	(a)	(b)
Inorganic Base %	2.5	6
Fat Soluble Base %	10	8
Polymer Base %	8	16
Flavour %	2	1
Sugar or Syrup %	41	52.5
Littesse	30	20
+		
Ondansetron %	1	1
Rolling compound %	5	5
+		
Ondansetron %	0.5	0.5

A 1 gram portion of gum will therefore contain 15mg of ondansetron 5mg available immediately delivered by the acidic rolling compound leaving 10mg to partition between the gum and the oral cavity.

It will be appreciated that the percentages of ingredients and that of ondansetron may be carried over a wide range, apparent to the skilled artisan and falling within the scope of the present disclosure.

Example 2

A chewing gum composition of ondansetron may also be formulated in accordance with US Patent 3,901,248 disclosed and incorporated fully herein by reference, wherein the ondansetron hydrochloride substitutes for the nicotine as in the disclosed cation exchange resin couples. In accordance with the disclosure US 3,901,248, the ondansetron will be complexed with an exchange resin preferably Amberlite IRP69. It will be appreciated that other cation exchange resins may also be used as practised by the art such as Amberlite IRP64, BIOREX 63, Amberlite IRC50, BIOREX 40, BIOREX 70, Duolite ES-65, Duolite ES 62, Chelex 100, CM Sepherdex C-25, SE Sepherdex C-25 and the like. The amount of ondansetron to constitute between 5% and 35% of the cation exchange complex weight.

A chewing gum is formed by mixing the ondansetron cation exchange complex to conventional chewing gum ingredients by conventional means known to the art. Typical chewing gum ingredients being commercial chewing gum bases such as Chicle, Jelutong, Lechi di Capsi, Soh, Siak, Katiau, Sorwa, Balata, Pendare, Perillo, Malaya, Percha, Dammar, Mastix, Vinapas, Dreyco, or any non-toxic polymer as used in the art of chewing gum manufacture, polyvinyl esters or polisobutylene and the like.

Softeners are added as desired examples of softeners being lecithin, lenolin, coconut oil preferably hydrogenated, cottonseed oil also hydrogenated, mineral oil, olive oil, paraffine wax, carnauba wax, candilla wax, steric acid, beeswax. Flavourings such as corn syrup, honey, sucrose, xylteol, saccharin, peppermint, sovelitol may be added as desired, the amounts to vary as guided by taste preferences of the intended consumer.

Bulking agents such as starch, calcium carbonate talc, defatted cocoa are used to make the physical properties of the gum more interesting to chew. It will be appreciated that an endless variety of chewing gum formulations exist which could deliver ondansetron in the intended circumstances. All of which full within the scope and spirit of the present disclosure.

Example 3

It may be desirable in some circumstances to reduce the amount of chewing required to release the ondansetron from the composition. In accordance with WO91/09599 disclosed and incorporated herein fully by reference a pharmacological agent may be presented with a cyclodextrin to create a non-irritant pastel or gum which releases the agent in a non-pH dependent manner. The preferred cyclodextrins for this purpose being β-cyclodextrin but also suitable are α- and γ-cyclodextrin as are trimethyl-β-cyclo dextrin, demethyl-β-cyclodextrin. The ondansetron is agitated with β-cyclodextrin to achieve an equilibrium of 10% ondensetron with β-cyclodextrin.

In the case of nicotine complexes with β-cyclodextrin one is directed to Anal. Chem. 1984, 56; 2827-2830. Based on the preparation of nicotine β-cyclodextrin the ondansetron-β-cyclodextrin may be prepared as follows;

Step 1 An aqueous solution of 3% wt/wt ondansetron with British Pharmacopoeia pure water is prepared.

Step 2 To each 100ml of this solution 30g of β-cyclodextrin are added.

Step 3 The mixture is stirred in a mechanical stirrer for 6 hours at room temperature.

Step 4 The mixture is now dried in either a drying oven at 35°C, or by accelerated freeze drying.

The powder obtained at the termination of the drying cycle will constitute β-CD-ondansetron, (β-cyclodextrin complex).

Tablets may now be made differing in minor respects to those of Carlson et al WO19/09599 incorporated herein fully by reference. An example of such a tablet being,

composition per tablet;

β-CD-ondansetron	80mg
Sorbitol powder	500mg
PEG 6000	20mg
Glycerine	5mg
Defatted cocoa	10mg
Peppermint flavour	0.5mg
Hydrogenated coconut oil	2mg
Coloring	optional

Tablets may be manufactured by the mixing of ingredients in suitable vessels in accordance with good manufacturing practice, the mixed ingredients being weighed and compressed into pellets of the desired form and shape.

Additionally chewing gums may be made wherein the β-CD-ondansetron complex is added to the bulk sweetner or other chewing gum component.

Example 4

Ondansetron may be used in conjunction with pyrodistigmine bromide (PB) or other carbamate as an antidote to alleviate nerve gas poisoning.

The ondansetron in accordance with the previous examples may be taken separately or may be formulated into an injection comprising the mixture of ondansetron and pyrodistigmine bromide a typical composition could comprise;

Ondansetron	4mg
Pyrodistigmine Bromide	10mg
Acqua distillata	2ml

(Injectable grade distilled water)

The compositions of ondansetron in accordance with examples 1,2,3, are packaged in a manner different from other pharmaceuticals to fabricate articles of manufacture for the claimed uses.

An overview of pharmaceutical packaging may be obtained in "Medical device packaging handbook" ed. D.O'Brien ISBN 0-8297-7698-4. This detailed work published 1990 reviews the current art. Of special relevance is Chapter 3. Carl D. MAROTTA, disclosed and incorporated herein fully by reference.

The present art considers the package of a pharmaceutical device to be an essential part of its design and dependent in the intended function.

None of the three categories of package requirement listed by Marotta satisfy the packaging requirements for the present articles of manufacture in full.

Important differences exist between the packaging requirements of the present articles of manufacture and those in the art.

Unlike pharmaceuticals for the clinic or hospital whose packaging must be capable of being opened manually without undue effort even by weak or ill persons, the articles of the present disclosure may be packaged by packaging which requires a knife or sharp object for their release, as would be available in combat.

Additionally the articles of manufacture of the present disclosure should be packaged in housing impervious to seawater and in housing which does not decay or rot after several exposures to immersion in sea water. Further the packaging must not only resist electrolytic corrosion itself but also must not corrode by electrolysis any part of a marine vessel. The packaging should at least in some circumstances resist negative pressure, as in aircraft especially high altitude military jets.

Further the packaging should in some circumstances be impermeable to Helium for use in diving bells and capable of resisting 12 atmospheres.

Still further the pharmaceutical compositions should be held rigid within the housing, of especial importance to combat troops in circumstances where unnecessary noise is undesirable.

The preferred package form is a preformed tight fitting plastic tray contoured to the shape of the chewing gum tablet.

Where Tyvek is used the lid and tray should both be of Tyvek and heat sealed around the parimeter. The small perforations in Tyvek are considered useful for aviation applications but not for underwater applications.

For general purpose use high density polyethylene HDPe for both tray and lid is ideal.

This strong material as a preformed tray and lid heat sealed to include the composition satisfies the packaging requirements.

It should be noted that both the lid and floor of the container should contain some corrugations to allow for barometric pressure adjustment. Further the lid and floor should be close fitting to the composition to ensure the package traps the minimum of air.

It will be appreciated that HDPe can be substituted for by nylon;. polypropylene; polycarbonate as would be obvious to the skilled artisan, keeping in mind the unusual physical requirements of the package and the range of physical environments it will have to withstand.

Further, detailed instructions for use of the present articles of manufacture may be printed in edible non-toxic ink on edible non-toxic paper such as rice paper and the said instructions to be packaged inside the sealed HDPe tray adjacent to the ondansetron itself.

It is envisaged that the chewing gum tablets be individually packaged in sealed HDPe containers and that each individual tablet be packaged with adjacent rice paper emergency instructions. The packaging of instructions adjacent to a pharmaceutical composition in this manner is not the practise of the current art.

It will be appreciated that the sealed HDPe containers each containing individually packaged ondansetron compositions together with instruction printed on rice appear may be further packaged in groups or separately housed in a container whose seal is less critical but whose integrity to water penetration and barotrauma is desirable.

Further printed instructions may be provided on the other container or contained within it.

Additional instructions or emergency advice may be included on the outside of the sealed HDPe container. Non-wettable paste ink is desirable for this use.

It will be further appreciated that the instructions and information provided with the pharmaceutical compositions of ondensetron contain information relating to survival in emergencies, signalling for help, staying calm, preventing dehydration, preventing hypothermia or any such survival information which may be considered useful, which information and packaging is substantially different from that normally associated with hospital or clinical use of ondansetron.

CLAIMS

(1) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of seasickness especially seasickness associated with TEMPSC (totally enclosed motor propelled survival craft) or small yachts, and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-)
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(2) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of apathy especially apathy associated with seasickness and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-)
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(3) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of dehydration during combat or civilian emergencies such as shipwreck and where the packaging material is of a type suitable for

military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(4) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of airsickness associated with military jet aircraft during manoeuvres involving fluctuating G forces or during training or combat, and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(5) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of space sickness and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for spacecraft or emergency use of the said agents.

(6) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for

therapeutic use in the treatment or prevention of Combat Related Stress disorder, CRS, or battle fatigue and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(7) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of neurological symptoms provoked by chemical warfare agents particularly the nerve gas SOMAN® and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(8) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of nausea provoked by chemical or biological warfare agents in circumstances where it may be hazardous to vomit and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(9) An article of manufacture comprising packaging material and a pharmaceutical agent or pharmaceutical composition of a pharmaceutical agent contained and protected by the packaging material, where the pharmaceutical agent or composition is intended for therapeutic use in the treatment or prevention of post traumatic stress disorder especially associated with combat or disasters, and where the packaging material is of a type suitable for military use or use in emergency situations and where the pharmaceutical agent is a racemic mixture of ondansetron of formula, R(+) and S(-) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl) methyl]-4H-carbazol-4-one, or compositions thereof, and where the packaging material contains or includes printed directions specific for combat, maritime, or aircraft emergency use of the said agents.

(10) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of seasickness especially seasickness associated with search and rescue in TEMPSC (totally enclosed motor propelled survival craft) or small yachts.

(11) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of apathy especially apathy associated with seasickness.

(12) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of dehydration during combat or civilian emergencies such as shipwreck.

(13) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of airsickness associated with military jet aircraft during manoeuvres involving fluctuating G forces during training or combat.

(14) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of space sickness.

(15) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of battle fatigue.

(16) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of combat stress reaction.

(17) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of neurological symptoms provoked by chemical warfare agents, nerve gas, particularly SOMAN.

(18) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of nausea, provoked by chemical or biological warfare agents in soldiers or civilians in circumstances where it may be hazardous to vomit.

(19) The use of ondansetron to obtain a medicine for intended therapeutic use in the prevention of or treatment of post traumatic stress disorder especially associated with combat or body handling or service personnel coping with civilian or military emergencies.

(20) The use of ondansetron to obtain a medicine for intended therapeutic use in the enhancement of the safety of persons where the medicine takes the form of a chewing gum.

(21) A pharmaceutical composition incorporating ondansetron in accordance with Claim 1 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(22) A pharmaceutical composition incorporating ondansetron in accordance with Claim 2 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(23) A pharmaceutical composition incorporating ondansetron in accordance with Claim 3 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(24) A pharmaceutical composition incorporating ondansetron in accordance with Claim 4 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(25) A pharmaceutical composition incorporating ondansetron in accordance with Claim 5 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(26) A pharmaceutical composition incorporating ondansetron in accordance with Claim 6 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(27) A pharmaceutical composition incorporating ondansetron in accordance with Claim 7 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(28) A pharmaceutical composition incorporating ondansetron in accordance with Claim 8 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(29) A pharmaceutical composition incorporating ondansetron in accordance with Claim 9 where the agent ondansetron is formulated as a chewing gum in accordance with exemplary embodiment number one.

(30) The use of a cation exchange resin complex of ondansetron to obtain a chewing gum.

(31) The use of a cation exchange resin complex of ondansetron to obtain a chewing gum for intended therapeutic use in the enhancement of safety of persons in danger, in combat, in warfare, in aviation, and in nerve gas poisoning.

(32) A composition of ondansetron and a cyclodextrein in accordance with Example 3.

(33) The use of cyclodextrein to obtain a complex of cyclodextrein and ondansetron to obtain a medicine for intended therapeutic use in the enhancement of safety, in combat, in warfare, in aviation and in nerve gas poisoning.

(34) The use of β-cyclodextrein complex of ondansetron to obtain a medicine for intended therapeutic use in the enhancement of safety at sea.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report) 30	Application number GB 9412950.9
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Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: DIALINDEX (MEDICINE, WPI, CAS-ONLINE)	Documents considered relevant following a search in respect of Claims :- 10, 11, 13 AND 14

Categories of documents

X:	Document indicating lack of novelty or of inventive step.	P:	Document published on or after the declared priority date but before the filing date of the present application.
Y:	Document indicating lack of inventive step if combined with one or more other documents of the same category.	E:	Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A:	Document indicating technological background and/or state of the art.	&:	Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0385517 A2 (BEECHAM) see Claims 4 and 11, Example 5	10, 11, 13 and 14
X	WO 92/04012 A1 (ALZA CORPN) see page 1 lines 11 to 16 and page 1 line 28 to page 2 line 6; Claim 1	10, 11, 13 and 14
A	Br J Clin Pharmacol (UK), 27/2, pages 147-157 (1989) (STOTT ET AL)	

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